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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,982	KAKIZUKA ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed on February 8, 2007, has been received and entered. Claims 1-3 have been amended.

Election/Restrictions

Applicant's election of claims 1-2 (group I) in the reply filed on June 20, 2006 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election was treated as an election without traverse (MPEP § 818.03(a)). Upon further review of the claims and specification, Examiner concluded that it would not be undue burden to examine all groups together. Accordingly, the restriction requirement was withdrawn and invention of group I and II were rejoined for examination purposes.

Claims 1-3 are under consideration.

Information Disclosure Statement

The reference JP 2002-58489 (AK in IDS) is considered to the extent it is presented in English. It is noted that only abstract has been considered, while rest of the disclosure that is in not in English language has not been considered.

Withdrawn-Claim Objections

The objection to claims 1-3 is withdrawn in view of amendments to the claims now reciting full text for the acronyms (ERRL1, ERR and MCAD).

New Grounds of Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by

Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claim 1 encompasses a method for screening a substance which serves as the active ingredient in a drug for obesity and or diabetes comprising treating cell or an animal with a candidate drug that fulfils one or more requirements selected from the list (a) increase transcriptional activity, (c) promote binding of ERR1 to ERR. Claim 2 is directed to a drug for obesity and or diabetes comprising as the active ingredient one or more substance as described in claim 1. Claim 3 is drawn to a transgenic mouse comprising in its genome a purified polynucleotide encoding a ligand factor ERRL1 for a nuclear receptor ERR and over expressing the ligand factor ERRL1.

Claims 1 and 3 are broad in scope. The following paragraph will outline the full scope of the claims: Claimed invention recites a method for screening therapeutic substance of obesity and or diabetes by treating any cell or any animal the promotes binding of ERRL1 to ERR and increases transcriptional activity of ERR. Claim 3 is directed to a transgenic mouse comprising polynucleotide encoding ERRL1 for a

nuclear receptor ERR and over expressing ERRL1 under the control of any promoter, wherein said mouse is lean and hyperphagic. These claims are broad in scope, encompassing any cell or animal for screening therapeutics for complex disease like diabetes and obesity. Furthermore, claims also embrace transgenic mouse that shows lean and hyperphagic phenotype for elucidating the mechanism of diabetes/obesity, the disclosure provided by the applicant, in view of prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other word each of those, aspect considered broad must be shown to a reasonable extent so that one of the ordinary skills in the art at the time of invention by applicant would be able to practice the invention without any undue burden being on such Artisan.

However, such broad disclosure does not demonstrate the information required by the Artisan to reasonably make and use transgenic mouse comprising ERRL1 in its genome with disclosed phenotype. The specification does not provide any specific guidance with how other transgenic mouse would be used for the screening or for further research. The specification does not provide any information as to what level of expression of the transgene in the parent of other species are required for obtaining the phenotype disclosed and effect of genetic background on the disclosed phenotype

The specification broadly discloses a method of screening drugs for obesity and or diabetes by using the expression and the activity of a ligand factor ERRL1 for a receptor estrogen receptor related receptor as an index. The specification discloses ERRL1 sequence after searching expression sequence tags for PGC-1 related molecule. It is noted that that Lin et al (J Biol. Chemistry 277, 1645-1648, 2002, art of

record) also reported cloning of a PGC-1 homologue named PGC-1β with only one amino acid difference from ERRL1 (see page 26 lines 11-22 of the specification). Furthermore, it is also noted that Applicants in a post filing publication related with instant invention have synonymously used the term ERRL1 and PGC-1β (see Kamei et al Proc Natl Acad Sci U S A. 2003; 100(21): 12378-83, art of record). The invention is based in part to a finding indicating that the ERRL1 function a protein ligand for ERRs and control energy expenditure in vivo (see discussion on page 34 lines 16-30 and page 33 lines 9-30).

As a first issue, claims are directed to a method of screening a therapeutic substance that serves as an agent for the treatment of obesity and or diabetes by treating any cell or animal with candidate substance that promotes binding of ERRL1 to ERR and increases the transcriptional activity of ERR. In the instant case, it is not clear how an artisan would measure the binding of ERRL1 to ERR and transcripional activity in any type of cells. In a pre and post filing art it is reported that PGC-1 mRNAs is present at very low levels in 3T3-L1 preadipocytes which is induced during adipocyte differentiation (see Fig. 1*B*), while Hentschke et al (Biochem Biophys Res Commun. 2002 20;299(5):872-9) reported PGC-1 is a coactivators of the orphan receptor ERRγ which is co expressed in heart, skeletal muscle, kidney, and brain. Thus, it is apparent that method set forth in claim 1 is not enabled for using any cell including yeast/ bacterial /any mammalian cells that may not be suitable for directly treating with an agent to measure the enhanced binding of ERRL1 to ERR or transcriptional activity as embraced by the breadth of claim 1. The specification discloses reporter plasmid having

an ERR responsive sequence or gal4 responsive sequence in the promoter region is co transfected into cultured cells with an expression vector of the full-length ERR protein or a fused protein of the ligand binding region of ERR with the DNA binding region of gal4, respectively. It is noted that a candidate substance is added to the cells and the activity of reporter gene in the extracted solution of the cultured cells is measured after several days (see Figure 3 and para 36). The specification also contemplate using the two hybrid method in cultured animal cells to measure the binding of ERRL1 to ERR by measuring the reporter gene activity in presence of candidate substance (see para. 37 of the specification). Prior to instant invention, it is generally known that exemplified method of yeast two-hybrid screen of protein-protein interactions results in high number of false positive (and false negative) identifications. Althogh, specific rate of false positive results is unknown, but Deane et al (Mol Cell Proteomics 1 (5): 349-56) concludes it may be as high as 50% (see abastract). The specification does not provide any guidance to overcome this art recognized problem for screening agent that prmotes binding of ERLL1 to ERR. It is also noted that as recited method of claim 1 does not set forth any active step that enbles an artisan to pratice the binding of ERRI1 to ERR. Furthermroe, breadth of claim 1 also embrace screening a therapeutic substance that serves as an agent for the treatment of obesity and or diabetes by treating any animal including wild type animal with candidate substance that promotes binding of ERRL1 to ERR and increases the transcriptional activity of ERR. Although, transcriptional activity of ERR could be determined in wild type animal, however, it is not apparent how treating any animal with candidate agent and then determining substance that promotes

biological activity set forth in claim 1 (a-b) would specifically indicate such agent to be specific for the treatment of diabetes and or obesity. It is noted that prior to instant invention, Hentschke et al disclose that ERRs have been implicated in a variety of developmental functions as different as placentogenesis and bone formation and in breast cancer (see page 873, col.1, para. 1 and reference therein). The specification does not provide any nexus between an agent that would promote the binding of ERRL1 to ERR or transcription of ERR that would be specific for obesity and or diabetes. In addition, it is emphasized that diabetes and obesity are complex disorders and involves interaction of multiple pathways. For instance, Maffei et al (Ann Ital Med Int. 2002 Oct-Dec; 17(4): 221-8) report Alstrom syndrome is a rare, autosomal recessive disorder characterized by retinal degeneration, obesity, non-insulin-dependent diabetes mellitus and kidney and heart failure. The Alstrom syndrome gene located on chromosome 2 that has been recently identified involves multiple organ systems with a complex interaction between pathways. Similarly, Aluclu et al (Neuro Endocrinol Lett. 2006 (6):691-4) also describe Wolfram syndrome (WS) which is an autosomal recessive disorder characterized by the association of juvenile-onset diabetes mellitus and optic atrophy. Aluclu et al disclose new mutation (c.1522-1523delTA, Y508fsX421) in WS1 gene in Wolfram syndrome that is responsible for early appearance of clinical features of Wolfram syndrome (abstract). It is noted that neither prior art nor instant specification, provide any nexus between transcriptional activity of ERR to obesity and or diabetes caused due to different autosomal recessive disorders. Thus, it is clear that method as recited in claim 1 would not screen agent that would be specific for the treatment of

diabetes and or obesity neither in any cell nor in any animal as embraced by the claim 1. In absence of any specific guidance and artisan would have to perform undue experimentation to first establish the nexus between claimed biological activity to specific condition of obesity and or diabetes.

As a second issue, instant claim 3 recite a transgenic mouse comprising polynucleotide encoding a ligand factor ERRL1 for a nuclear receptor ERR in its genome and over expressing ERRL1 wherein mouse is lean and hyperphagic. The specification teaches generation of transgenic mouse using CAG promoter (see figure 4A). It is noted that specification contemplates transgenic animal of the invention is useful not only as a control in the screening method but also as a model animal in the elucidation of an anti-obesity or anti-diabetic mechanism at the whole body level (see para. 42 of the specification). The specification does not enable one of skill to screen for an agent for use in the treatment of obesity or diabetes using a transgenic mouse over expressing ERRL1 as a positive control or a wild type mouse as contemplated by the specification. It is emphasized that diabetes is characterized by a changes in glucose homeostasis include hyperinsulinemia, hyperglycemia, increased weight gain or decreased muscle glycogen. The specification teaches that agents capable of promoting binding an ERRL1 to ERR or increasing the transcriptional activity can be identified by administering the agent to the transgenic mouse and assessing the animal (Specification see para 68-69). However, 102 mutations of 64 different genes cause hyperglycemia in mice (see MGI pages titled "Mammalian Phenotype Ontology Annotations" for hyperglycemia ; http://www.informatics.jax.org/searches/Phat.cgi?id=

MP:0001559 and ttp://www.informatics.jax.org/javawi2/servlet/ WIFetch?page=mpAnnotSummary&id=MP:0002138). Hyper insulinemia is generic to 94 mutations of about 57 genes and increased weight gain is generic to 14 mutations of 11 genes. (Increased weight gain is defined by MGI as "greater increase in body weight over existing weight when compared to the average increase in weight on the same diet, with equal energy intake" which equivalent to increased weight gain on a high fat diet as claimed because it would occur on a normal or high fat diet.) Therefore, one would not be able to tell whether the agent was promoting the activities set forth in claim 1 or whether the agent was modulating one of the 64 other genes that affect hyperglycemia, hyperinsulinemia, etc. As such, it would have required one of skill undue experimentation given the teachings in the specification to determine whether the agent had any effect on the activities set forth in claim 1 resulting in identification of agent for the treatment of obesity and or diabetes. Furthermore, prior to instant invention, it is generally known that the art of transgenic mouse and resulting phenotype are sensitive to factors such as integration site of the transgene, copy number as well as genetic background of the mouse used. This observation is supported by Sigmund (Sigmund et al Arterioscler Thromb Vasc Biol. 2000 ; 20(6):1425-9) that states that in regards to mice "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype." (pg, 1425, col. 1, Introduction). These "epigenetic" effects can dramatically

alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction). Sigmund concludes by stating that "in the absence of inbred strains, there is no optimal set of experimental and control conditions that normalizes the epigenetic effects of unlinked loci," and that each transgenic mouse strain must be assessed as to whether the phenotype observed is due specifically to the targeted modification or is affected by other loci (pg. 1428, col. 1, Guidelines). This is due in part to the fact that expression levels do not always correlate with the number of transgene copies integrated (Leiter et al. (2002) Diabetologia 45:296-308;pg. 304, col. 1). Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene (pg. 303, col. 2). Further, Leiter et al (Diabetologia. 2002; 45(3):296-308, art of record) while reviewing the transgenic mice focuses on certain complications inherent in the methodologies from unexpected contributions from the genetic background states "multiple lines of transgenic mice should be produced and analyzed since transgene insertion is essentially random and each line usually conations different transgene copy number. Comparisons of multiple lines are essential for determining whether a transgene's effect is an intrinsic property of its function instead represents insertational mutagenesis or high copy number generated phenomena" (see page 304, paragraph 1). Furthermore, Finck et al (Journal of Clinical Investigation 116:615-622, 2006) in a post filing art describe "importance of PGC-1α and PGC-1ß as boosters of nuclear receptor (NR) function for understanding the fundamental connections between alterations in the external environment and adaptive metabolic responses of striated

muscle and liver. He evinces a positive outlook but concludes that, "the role of these powerful and highly inducible co-activators as protectors versus mediators of disease has not been well defined and will require additional translational studies bridging animal models, such as conditional genetically modified mouse models (see page 620, column 2, last paragraph). Thus, cited art clearly suggest the role of ERRL1 *in vivo* is still a subject of active research. The lack of guidance, breadth of claims, the level of skill in the art and state of the art at the time of claimed invention was made, it would have required undue experimentation to make and/or use the inventions as claimed. Here, the claims broadly encompass transgenic mouse that is transgenic for polynucleotide encoding ERRL1 which could be used as model to elucidate of an anti-obesity or anti-diabetic mechanism at the whole body level (see para 42 , last line of the specification). Thus, in order to use the mice, the artisan would need to perform further research upon the claimed mice in order to determine the correlation between the knock in and the observed phenotypes relating to diabetes or obesity. Furthermore, use of instant transgenic mouse as control would also be not specific, as the skilled practitioner would be reduced to guessing as to whether phenotype exemplified in the specification is due to over expression of ERRL1 or due to other factors as discussed above (supra). Such guessing would require an artisan to engage in extensive and undue experimentation.

In view of the lack of teachings or guidance provided by the specification with regard to method of screening agents for the treatment of obesity and or diabetes and transgenic mouse comprising in its genome ERRL1. The lack of teaching or guidance

provided by the specifications to overcome the art recognized unpredictability of using any cell for screening method, nexus between biological activity and obesity and diabetic condition and phenotype obtained in the transgenic mouse and for the specific reasons cited above it would have required undue experimentation for an artisan of skill to make and use the invention as claimed.

Response to Arguments

Applicants arguments filed February 8, 2007have been fully considered but they are not persuasive. Applicants argue that specification fully describes and enables an tn vitro screening method using cells. Applicants also assert that the specification also provides in vitro working examples demonstrating the interaction of ERRL and ERR in a cell. With respect to in vivo method applicant argue that transgenic animal is not essential to the claimed screening method. The animal used in the in vivo screening method is wild type. The transgenic animal may be used as a control in the in vivo screening method. Applicants further assert that it may also be model animal in the elucidation of an anti-obesity or anti-diabetic mechanism at the whole body level (see page 5 of the arguments).

In response, it is emphasized that the breadth of claim 1 embraces screening for a substance for the treatment of obesity and or diabetes by treating cell and identifying agent that has property set forth in claim 1. However, method as claimed doesnot provide any active step that binding of ERRL1 to ERR and transcripional activity in any type of cells could be measured as broadly recied in the claim. In pre and post filing art it is reported that PGC-1 mRNAs is present at very low levels in many cells (3T3-L1

preadipocytes which is induced during adipocyte differentiation) thus it is apparent that method set forth in claim 1 is not enabled for using any cell including yeast/ bacterial /any mammalian cells that may not be suitable for directly treating with an agent to measure the enhanced binding of ERRL1 to ERR or transcriptional activity as embraced by the breadth of claim 1. In addition, it is also noted that prior art disclose that ERRs have been implicated in a variety of developmental functions as different as placentogenesis and bone formation and in breast cancer (see page 873, col.1, para. 1 and reference therein, supra). The specification does not provide any nexus between an agent that would promote the binding of ERRL1 to ERR or transcription of ERR that would be specific for obesity and or diabetes. Thus, any agent obtained by screening solely based on its effect on ERR may not be specific to diabetes and or obesity. Thus, it is clear that an artisan would have to further undue experimentation to practice the method to screen substance for the treatment of obesity and or diabetes. Applicants also argue that disclosed transgenic animal would serve as positive control or could be used for studying the anti-obesity or anti-diabetic mechanism. In response, it is emphasized that transgenic mouse and resulting phenotype are sensitive to factors such as integration site of the transgene, copy number as well as genetic background of the mouse. It is not clear whether the lean and hyperphagic phenotype exemplified in the instant application is specific due to over expression of ERRL1 or due to genetic background. In addition, diabetes and obesity are complex disorders and involves interaction of multiple pathways. Examiner has cited references to show rare diseases that are characterized by obesity, non-insulin-dependent diabetes mellitus and

involves multiple organ systems with a complex interaction between pathways. The specification does not provide any nexus between ERRL1 and diabetes and or obesity caused by multiple pathways. In absence of any specific correlation to any disease or condition an artisan would have to perform further research upon the claimed mice and the observed phenotypes relating to diabetes or obesity. If claimed transgenic mouse require further research for the purpose of establishing mechanism as argued by the applicants, then it is clear that an artisan would not know how to make use of the invention as claimed. It is emphasized that use of instant transgenic mouse as control would also be not specific, as the skilled practitioner would be reduced to guessing as to whether phenotype exemplified in the specification is due to over expression of ERRL1 or due to other factors as discussed above (supra). Such guessing would require an artisan to engage in extensive and undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instant claims embrace a pharmaceutical composition for the treatment for obesity and/or diabetes comprising as the active ingredient one or more substances specified by the method that increases the transcriptional activity of the nuclear receptor ERR and or promoting the binding of ERRL1 to ERR.

Vas-cath Inc. v. Mahurkar, 19USPQ2d 11 11 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1 117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification has provided the description of candidate substance that includes an organic or inorganic substance, a protein, a peptide, a polynucleotide, an oligonucleotide and the like, which are either unknown or known (see para. 33 of the specification). However, The specification fails to describe candidate substance showing contemplated biological activity fall into the genus. Since the specification fails to disclose adequate number of candidate agent that increases the transcriptional activity of the nuclear receptor ERR and or promoting the binding of ERRL1 to ERR, it is not possible to envision the broadly claimed compositions showing contemplated biological activity of treating obesity and or diabetes. One cannot describe what one

has not conceived. It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential structures and function of molecules that are essential for a genus of candidate substance for performing contemplated functions. The specification does not discloses the knowledge in the prior art and/or a description as to the availability of a representative number of species of such candidate agent, that must exhibit the disclosed biological functions as contemplated by the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements or structure, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming an unspecified genus of agent capable of performing contemplated functions of promoting binding of ERRL1 to ERR and increasing the transcriptional activity that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so does not comply with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure

of a genus of agents that must be capable of performing contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 1-2 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Instant claims uses any cell of any origin and species for screening drugs for the treatment of diabetes and obesity, but the does not set forth any steps involved in method/process, it is unclear what method /process applicant is intending to encompass. The omitted steps are: whether cells are transfected with ERR or ERRL1 or with any reported gene. The claim merely recites a

method of screening agent for the treatment of diabetes or obesity without any active, positive step delineating how binding ERRL1 to ERR is actually measured in any cell and how data will be compared to conclusively suggest that resulting biological effect is due to test agent and not due to experimental condition. Claim 2 depends on claim 1. Appropriate correction is required.

Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recite a limitation "increasing the transcriptional activity of ERR as same as action of ERRL1 for ERR". The recitation is indefinite to the extent it is not apparent whether candidate substance increases the transcriptional activity of ERR or it is comparable to the action of ERRL1 for ERR. The term "as same as the action of ERRL1 for ERR" does not further clarify the property of the candidate substance. Claim 2 depends on claim 1. Appropriate correction is required.

Withdrawn-Claim Rejections - 35 USC § 102

Claim 3 rejected under 35 U.S.C. 102(e) as being anticipated by Spiegelman et al (US Patent publication no. 2003/0124598, dated 7/3/2003, effective filing date 11/09/2001) is withdrawn since cited art does not explicitly teach transgenic mouse over expressing ERRL1 that is lean and hyperphagic.

Claim 3 rejected under 35 U.S.C. 102(b) as being anticipated by Spiegelman et al (WO00/32215, dated 06/08/2000) is withdrawn as cited art does not explicitly teach transgenic mouse over expressing ERRL1 that is lean and hyperphagic.

New Grounds of Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2 are rejected under 35 U.S.C. 102(e) as being anticipated by Spiegelman et al (US Patent publication no. 2003/0124598, dated 7/3/2003, effective filing date 11/09/2001, IDS).

Claims are directed to a method of screening a substance which serves as the active ingredient in a drug for obesity and or diabetes comprising treating cell or an animal with a candidate drug that increase the expression level of ERRL1. (Claim 2 is directed to a drug for obesity and or diabetes comprising as the active ingredient one or more substance as described in claim 1. Claim 3 is drawn to a transgenic nonhuman animal comprising in its genome a purified polynucleotide encoding a ligand factor ERRL1 for a nuclear receptor ERR and overexpressing the ligand factor ERRL1.

Spiegelman et al teach an isolated nucleic acid molecule PGC-1beta, which encode novel PGC-1 related co-activator molecules (abstract). It is noted that the isolated nucleic acid molecule disclosed by Spiegelman may comprise a nucleotide sequence, which is at least about 50- 99.99% or more identical to the entire length of the nucleotide sequence (page 2 and 3, paragraph 20). It is emphasized that Applicants in a post filing publication related with instant invention have synonymously used the term ERRL1 and PGC-1β (emphasis added, *supra*). Therefore, nucleic acid sequence disclosed by Spiegelman would meet the claim limitation of instant invention. Spiegelman et al also teach agent that modulates expression of PGC-1beta (ERRL1) by modulating transcription of a PGC-1 beta (ERRL1) meeting the claim 1(b) limitation (see para. 24 and 193). It is noted that Figure 7A-7D shows the results of transcriptional analysis of the coactivation of nuclear receptors NRF1 (FIG. 7C) by murine PGC-1.beta. Spiegelman teaches several method of screening drug that modulate expression of PGC-1 beta including a method to identify other proteins including nuclear receptors or other transcription factors, which bind to or interact with PGC-1.beta using two hybrid system but did not explicitly teach binding with ERR. In addition, Spiegelman also teach therapeutic agents including peptides, peptidomimetics, amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds that modulates the expression or activity of PGC-1 beta (see paragraph 177 and 179), thus these agents would be same agent as one recited in claim 2. Accordingly, Spiegelmen anticipates claims 1-2.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Spiegelman et al (WO00/32215, dated 06/08/2000, IDS).

Spiegelman et al teach an isolated nucleic acid molecule PGC-1, which encode proteins that could modulate various adipcyte-associated activities (see abstract). It is noted that that isolated nucleic acid disclosed by Spiegelman could be at least 50-95% or more homologous to nucleic acid sequence of PGC-1. It is emphasized that Applicants in a post filing publication related with instant invention have synonymously used the term ERRL1 and PGC-1β (emphasis added). Thus, a portion of nucleic acid sequence disclosed by Spiegelman would meet the claim limitation. Spiegelman et al also teach a method for identifying a compound that stimulates the interaction of PGC-1 protein with a target molecule (see page 12, line 19-23, claim 21-22). The binding of target molecule to the PGC-1 protein to form complex is also contemplated meeting the claim 1 limitation (see page 12, lines 24). Spiegelman also discloses TRbeta/RXR combination alone induced very little transcription even in presence of ligand, however the combination of PGC-1 and TR beta/RXR alpha enhanced trans activation in a ligand dependent manner (see pages 80 lines 5-15). Spiegelman describes that transcriptional assay is useful for screening compounds which modulate the function of PGC-1 (ERRL1) alone and or in combination with PPAR gamma. Thus, it is apparent that method of Spiegelman inherently would teach compounds that increase the transcriptional activity of ERR as same action of ERRL1 for ERR as required by claim 1 (b). In addition, Spiegelman also teach therapeutic agents including polypeptides, nucleic acid molecule and antibodies that could be used for a method of treatment (see

page 57, lines 17-20). It is noted that the method of independent claim, claim 1 recite one steps: (a) treating cell or animal with candidate substance enhancing the transcriptional activity of ERR. Accordingly, claim 1 is anticipated by Spiegelman et al because steps recited in the invention are the same as those taught by the cited arts.

Accordingly, Spiegelman anticipates claims 1-2.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Scheen et al (Diabetes Metab Res Rev. 2000; 16(2):114-24) .

Claim 2 is product by process claim.

Scheen et al teach a number of pharmaceutical composition including Sibutramine and orlistat that promotes weight loss and improves blood glucose control in obese diabetic patients (see abstract and the entire article for all the different pharmaceutical composition). Since the composition of cited reference has similar pharmacological activity as one recited in claim 2 therefore, composition disclosed by Scheen would essentially have same characteristics as one expected in agents obtained after screening the drug using the method exemplified in the instant application. Accordingly, Scheen et al anticipate claim 2.

It is noted that claim 2 is a product by process claim. Where, in the instant cases, the claimed and prior art products are identical or substantially identical, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness'

under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). Further see MPEP § 2113, "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (Citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.).

Response to Arguments

Spiegelman et al (US Patent publication no. 2003/0124598, dated 7/3/2003, effective filing date 11/09/2001) and (WO00/32215, dated 06/08/2000).

Applicant's arguments filed February 8, 2007have been fully considered but they are not persuasive. Applicants argue that prior art teaches a method for screening a substance affecting ERRLI/PGC-1beta. However, the amended claims relate to interaction between ERRL I and ERR. In fact, the method of amended claim I relies on this interaction between ERRLI and ERR. These properties are relied upon in the method of the present invention for determining the substance to be used as the active ingredient. Applicants assert that Spiegelman reference fails to disclose or suggest present invention.In response, It is noted that as recited claim 1 require only one active method step that includes treating cell or animal with candidate substance and specifying the one of the property of the target ingredient. In the instant case, Examiner would agree that cited reference do not teach the a agent that promotes binding of ERRL1 and ERR but it is emphasized that cited reference teach agent that modulates expression of PGC-1beta (ERRL1) by modulating transcription of a PGC-1 beta (ERRL1) (see para. 24 and 193). In addition, Spiegelman et al show the results of transcriptional analysis of the co activation of nuclear receptors (FIG. 7A-D, para 64 and 193) by murine PGC-1beta. Since ERRL1 is ligand for ERR and therefore any agent that would enhance transcription for ERRL1 would inherently enhance transcriptional activity for ERR. It is reasonable to state that Spiegelman teaches methods of screening drug that modulate PGC-1 beta activity could be accomplished by monitoring the interaction with and/or co activation of a known target molecule (e.g., a nuclear receptor or HCF), by monitoring the autonomous transcriptional activity of PGC-1.beta (see para. 193). Furthermore, in absence of any other active method step other than treating

agent with to candidate agent that distinguishes the claimed method step with one disclosed by Spiegelman, the method disclosed in cited art clearly anticipate the method of claim 1. Furthermore, agents disclosed by Spiegelman would have similar pharmacological activity as one recited in claim 2 therefore, composition disclosed in cited art would essentially have same characteristics as one expected in agents obtained after screening the drug using the method exemplified in the instant application. It is emphasized that claim 2 is a product by process claim. Applicants argument of transgenic mouse disclosed in cited art does not teach the phenotype is persuasive and therefore rejection pertaining to claim 3 is withdrawn

Conclusion

No Claims allowed.

Spiegelman et al (US Patent publication no. 2003/0124598, dated 7/3/2003, effective filing date 11/09/2001).

Spiegelman et al (WO00/32215, dated 06/08/2000).

WO/00/26365 and JP 2002-58489 (document AJ and AK, IDS)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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